**DISSERTATION**

***on***

# A COMPARATIVE STUDY OF THE EFFICACY OF ORAL CLONIDINE AND ORAL ATENOLOL IN ATTENUATING THE HEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION

**M.D. DEGREE EXAMINATION**

**BRANCH -X**

**(ANAESTHESIOLOGY)**


**THANJAVUR MEDICAL COLLEGE**

**THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY**
**CHENNAI**
**SEPEMBER 2006**

# CERTIFICATE

This is to certify that this Dissertation entitled, "**A COMPARATIVE STUDY OF THE EFFICACY OF ORAL CLONIDINE AND ORAL ATENOLOL IN ATTENUATING THE HEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION**" is the bonafide record of work done by **Dr.VANMATHY.V**, submitted as partial fulfillment for the requirements of M.D. Degree Examinations Branch X,ANAESTHESIOLOGY, September 2006.


**Dr.A.L.MEENAKSHI SUNDARAM, M.D.,**
PROFESSOR,
Department of Anaesthesiology
Thanjavur medical college,
Thanjavur.

**Dr.R.MUTHUKUMARAN, M.D.,**
PROFESSOR AND HEAD,
Department ofAnaesthesiology,
Thanjavur Medical College,
Thanjavur.


**THE DEAN,**
Thanjavur Medical College,
Thanjavur

# ACKNOWLEDGEMENT

I am extremely thankful to our beloved Dean, Thanjavur Medical College, for granting me permission to undergo this study in Thanjavur medical college Hospital.

I am very grateful to our Professor and Head of the Department of Anaesthesiology, **Dr.R.MUTHUKUMARAN, M.D.**, for his moral support, philosophic guidance and constant help to undergo this study.

I am deeply indebted to my professor **Dr. A.L. MEENAKSHI SUNDARAM**, **M.D**., for his constant help and guidance to complete this study.

I am deeply indebted to my assistant professor **Dr.S.UTHIRAPATHI,M.D.,** for his invaluable guidance, perspectives, assortment of emerging views, constructive criticisms throughout the period of study.

I am extremely thankful to **Dr.THENMOZHI,M.D.,** and other Assistant Professors of Anaesthesiology for their guidance throughout the study.

I extend my sincere thanks to all the staff members ,fellow postgraduates and theatre technicians in my department for having helped me in every possible way.

I also thank our patients without whom the study would not have been possible.

I owe my thanks to almighty for successful completion of the study.

# CONTENTS

# INTRODUCTION

Securing the airway by means of endotracheal intubation is the sine qua non of our modern day general anaesthetic practice. The advantage of doing so have been emphasized, elucidated and extolled over these years.

But, endotracheal intubation is not entirely harmless and we come across many number of complications associated with it ranging from relatively minor to the seriously grave and potentially life threatening ones which would occur in susceptible patients.

Though these complications could be traced down to any of the many procedures that are part and parcel of the sequence of induction of anaesthesia and intubation, laryngoscopy and endotracheal intubation are the most powerful noxious stimuli which require a deeper level of anaesthesia than that is needed for surgical incision[1].

In anaesthesia, circulatory stimulation during tracheal intubation results from both direct laryngoscopy and placement of the tube in the trachea. These stimuli often evoke sympathoadrenal responses characterized by alterations in systemic arterial

pressure, heart rate , cardiac rhythm, ST segment changes, pulmonary oedema and rupture of cerebral aneurysm[2]. In anaesthetized humans, the usual circulatory responses to laryngeal and tracheal stimulation are tachycardia and systolic hypertension. When planning the anaesthetic induction, these effects must be blunted to whatever degree is possible, especially, if the patient is in a high risk population like patients with uncontrolled hypertension, coronary artery disease, asthma, elevated intracranial pressure, cerebral aneurysm etc[1].

Different techniques have been used to attenuate this hemodynamic response to laryngoscopy and intubation. These include topical anaesthesia of the oropharynx[3], intravenous lignocaine[3], intravenous fentanyl[4,5], alfentanil[5], sodium nitroprusside[6], beta-adrenergic blocking drugs[7,8,9], alpha-2-adrenergic agonists[10], alpha and beta-blockers, calcium channel blockers etc.

Prof. Ward and king (1960) in their study documented myocardial ischemic changes due to reflex sympathoadrenal response with a mean increase in systemic pressure of about +40 mm of Hg even in normotensives following laryngoscopy and endotracheal intubation. Prys-Roberts et al (1971)[2] showed that this response is even more exaggerated in hypertensive individuals.

Considering all these factors, attenuation of hemodynamic response to

laryngoscopy and endotracheal intubation will be a laudable objective and is definitely indicated.

In our study that was carried out in the department of Anaesthesiology, Thanjavur Medical College and Hospital, we compared the efficacy of oral clonidine and oral atenolol with a control group to determine how effective they are in attenuating the cardiovascular stress response to laryngoscopy and tracheal intubation.

# AIM OF THE STUDY

The present study was done to compare the effectiveness of oral clonidine and oral atenolol in attenuating the hemodynamic response to laryngoscopy and endotracheal intubation.

# PHYSIOLOGIC AND PATHOPHYSIOLOGIC RESPONSES TO DIRECT LARYNGOSCOPY AND INTUBATION

Direct laryngoscopy and tracheal intubation are both potent stimuli that may instigate an intense autonomic response[11]. Tracheal intubation alters respiratory and cardiovascular physiology by reflex response and by the physical presence of endotracheal tube. Although these circulatory responses are transient and of little consequence in patients with normal circulatory system, it could have an adverse effect in patients with poorly controlled hypertension, critical myocardial ischemia or those with raised intracranial pressure[1].

## CARDIOVASCULAR RESPONSE:

This transient, variable and unpredictable response is mediated by both sympathetic and parasympathetic nervous system. Bradycardia seen in infants and small children during direct laryngoscopy and intubation is the autonomic equivalent of laryngospasm response in adults. This reflex is mediated by an increase in the vagal tone at the sinoatrial node and is virtually a monosynaptic response to noxious stimuli in the airway.

The more common response to tracheal intubation is hypertension and tachycardia. This pressor response is mediated by sympathetic efferent via the cardio accelerator nerves and the

sympathetic chain ganglia[12]. The polysynaptic nature of pathways from the IX (Glossopharyngeal N) and X (vagus Nerve) nerve afferents to the sympathetic nervous system via the brainstem and spinal cord results in a diffuse autonomic response which includes widespread release of nor-epinephrine from the adrenergic terminals and from the adrenal medulla. One other reason for the hypertensive response is due to activation of renin – angiotensin system with the release of renin from the renal juxta-glomerular apparatus, which is an end organ innervated by adrenergic nerve terminals.

**BRONCHOMOTOR RESPONSE :**

Mechanical stimulation of the epipharynx, laryngopharynx and tracheobronchial tree causes [12]

i. Glottic closure reflex (laryngospasm) which is a brisk motor response,
ii. Reduction in dead space,
iii. Increase in airway and total lung resistance,
iv. Bronchospasm which is a reflex response to intubation and
v. Reduction in cough efficiency.

# METHODS TO ATTENUATE CIRCULATORY RESPONSES TO LARYNGOSCOPY AND INTUBATION

1) **Deepening of general anesthesia:**

Volatile anaesthestic agents can be used to deepen the plane of anaesthesia. MAC intubation is 30% higher than MAC incision.

**2) Shortening the duration of laryngoscopy to less than 15 seconds because longer the duration more is the pressor response[3].**

**3) Short acting Opioids.**

Fentanyl [4,5]– 2-5 microgram per kg, 3 minutes prior to induction.

Alfentanil[5] – 15 –30 microgram per kg just before induction.

Sufentanil – 10-30 microgram per kg, 3 minutes prior to induction.

Remifentanil[13]- 1-2 microgram per kg just before induction.

**4) Lignocaine.**

Intravenous lignocaine[14] 1.5 milligram per kilogram administered 90 seconds prior to induction of anaesthesia or topical administration of Laryngotracheal lignocaine[3] 2 milligram per kilogram immediately before placing the tracheal tube can be used.

**5) Vasoactive Substances.**

a) Nitroglycerin - 2 microgram per kilogram 15 seconds prior to laryngoscopy,

b) Sodium nitro prusside[6] - 1-2 microgram per kilogram 15 seconds prior to laryngoscopy briefly decreases vascular tone but the exact dose required for each patient is difficult to determine.

**6) Adrenergic Blockers.**

**a) Alpha and beta blockers:**

Labetolol – 100 to 250 µg/kg given intravenously atleast 3 minutes prior to intubation.

**b)Beta blockers:**

Esmolol[7,9] – 1 to 2 milligram per kilogram given intravenously about 15 seconds prior to induction of anaesthesia.

Propranolol[8] - 0.5 to 1 milligram given intravenously about 4 minutes to induction of anaesthesia.

Metoprolol[9]- 4 milligram as an intravenous bolus about 3 minutes prior to induction of anaesthesia.

Mechanism of action of beta blockers is by their negative inotropic and chronotropic action on the heart which prevents the increase in heart rate and blood pressure increase in response to stress or noxious stimuli[15]. Cardio selective beta blockers are the most useful.

**c) Calcium channel blockers :**

Nifedipine, verapamil, diltiazem can be used.

Verapamil is effective among the calcium- channel blockers to blunt the hypertension and tachycardia seen with intubation.

**d) ACE inhibitors :**

Captopril or enalapril can be given 45 minutes prior to induction.

**e) Alpha-2 agonists:**

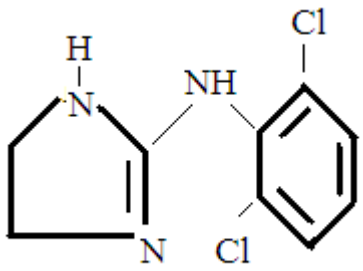
Clonidine[10] 4 to 5 microgram per kilogram orally 60-120 minutes prior to intubation. Dexmedetomidine and mivazerol are also useful.

Mechanism of action of alpha-2 agonists is by decreasing central sympathetic outflow, increasing the parasympathetic tone and by decreasing circulating noradrenaline concentrations[15].

# PARMACOLOGY OF CLONIDINE

Clonidine is a prototype, partially selective alpha-2 adrenoreceptor agonist (alpha-2: alpha-1 = 220:1). It is a centrally acting imidazole compound. It was synthesized in the early 1960s as a vasoconstricting nasal decongestant[15].

**STRUCTURAL FORMULA:**




**MOLECULAR FORMULA:**

(2-(2,6- dicholorophenylamino)-2-imidazoline)

**PHYSICAL PROPERTY:**

Molecular weight – 266.56

**PREPARATIONS:**

1. Tablets – 0.1mg, 0.15mg, 0.2mg, 0.3mg
2. Injection (Parenteral) – 0.15mg/ml ampoule (1ml)

3. Injection (Preservative Free): For epidural and spinal injection (0.1mg/ 1ml)
4. Transdermal therapeutic patch releases

   0.1mg/ 24 hours

   0.2mg / 24 hours

   0.3mg / 24 hours

**ROUTES OF ADMINISTRATION:**

It can be given as oral tablets, intravenous injection, Subarachnoid or epidural injection, as an additive for regional nerve blocks and intravenous regional anesthesia.

**PHARMACOKINETICS:**

Oral Clonidine is well absorbed with a bioavailability of nearly 100%. The onset of action starts from 30 to 60 minutes. The peak effect is between 60 to 120 minutes and its action lasts for up to 8 hours[15]. Clonidine has a low to moderate protein binding capacity (20 – 40%). It has an elimination half-life of about 6 to 24 hours with a mean of about 12 hours. The elimination half life is increased up to 40 hours in patients with renal dysfunction.

There is good correlation between the plasma concentration of clonidine and its pharmacological effects.

## METABOLISM AND ELIMINATION:

Nearly 50% of clonidine is eliminated unchanged in the urine and remaining drug undergoes hepatic biotransformation. Biliary and faecal excretion is responsible for 20% of drug elimination.

## PHARMACODYNAMICS:

| Plasma Concentration of clonidine (mg/ml) | Pharmacological effects |
|---|---|
| About 1 | Salivary flow reduced |
| > 1.5 – 2 | Sedation to Sleep |
| Up to 1.5 - 2 | Hypotension |
| >2 | Vasoconstriction to Hypertension |

Clonidine acts on various systems in the body.

### CARDIOVASCULAR SYSTEM:

Clonidine has got both central action and peripheral action._____

### Central action: -

Activation of central alpha-2 adrenergic receptors in medullary vasomotor center inhibits the release of nor epinephrine from the adrenergic neurons and reduces sympathetic outflow from the CNS. Further, there is reduced discharge from the

postganglionic fibres of cardiac nerves and an increase in parasympathetic tone[15].

This results in decrease in blood pressure, heart rate, cardiac output and peripheral vascular resistance.

Nucleus tractus solitarius, the site that modulates the autonomic control including vagal activity is an important central site for the action of Clonidine[15].

Other proposed sites of action are locus coeruleus, dorsal motor nucleus of vagus and nucleus reticularis lateralis.

Reduction in sympathetic tone is accompanied by lowering of plasma renin activity, decrease in renal vascular resistance and maintenance of renal blood flow even when the blood pressure is lowered. Vasopressor centers of the brainstem retain their sensitivity to baroreceptor control and hence postural hypotension is considerably less than the effects of drugs that act on the autonomic ganglia and peripheral adrenergic neurons.

The absence of a fall in blood pressure when Clonidine is given to tetraplegic with complete spinal cord transection above the level of sympathetic outflow also suggests a central site of hypotensive action[15].

## Peripheral action:

These are mediated by inhibition of norepinephrine release from the peripheral prejunctional nerve endings and by decreasing plasma concentration of norepinephrine.

**CORONARY CIRCULATION:**

The direct effect of alpha-2 agonists on coronary vasculature is vasoconstriction. However, this is offset by the generalized reduction in sympathetic outflow**.**

**CENTRAL NERVOUS SYSTEM**

Clonidine has got a sedative and anxiolytic action[16]. The sedative effect of clonidine may be due to decreased tonic activity of the locus coeruleus which modulates the stimuli arriving in the central nervous system[15]. It has got a potent spinal and supraspinal analgesic action. Clonidine has got opioid sparing effect and it reduces the anaesthetic requirements. It reduces the MAC value of halothane and isoflurane[17]. It suppresses physiological and psychological symptoms after withdrawal of opioid, alcohol, benzodiazepines, barbiturate, nicotine etc. in addicted patients

**RESPIRATORY SYSTEM:**

Clonidine has minimal bronchodilating and respiratory depressant activity.

**ENDOCRINE SYSTEM:**

Clonidine suppresses insulin secretion, decreases utilization of glucose by tissues and may cause hyperglycemia. It inhibits the secretion of renin.

**GASTROINTESTINAL SYSTEM:**

Clonidine decreases salivary flow. It prevents intestinal ion and water secretion in the large bowel.

## USES:

**i) Preanaesthetic medication:**

Dose: 3-5microgram per kilogram orally 60 – 120 minutes prior to induction of anaesthesia. When given as a premedicant, clonidine provides sedation[16] , anxiolysis[16], antisialogogue effect, decreases the dose of induction agent, attenuates the hemodynamic response to laryngoscopy and intubation[10,16], decreases the intraoperative lability of blood pressure and heart rate, decreases MAC of inhalation agents[17,18], provides analgesia, reduces narcotic requirements[19] and decreases postanaesthetic shivering[20].

**ii) Spinal and epidural analgesia:**

Preservative free clonidine injected epidurally (2 to 10 microgram per kilogram diluted) or into the subacachnoid space (0.3 – 3 microgram per kilogram) produces dose dependant analgesia. It acts on the substantia gelatinosa of the spinal cord, inhibits substance P release and nociceptive neuron firing produced by noxious stimuli.

**iii) Prolonging the effect of regional anesthesia:**

oral clonidine prolongs the duration of tetracaine spinal anaesthesia and when added to local anaesthetic solution prolongs brachial plexus block and caudal analgesia.

**iv) Treatment for post anesthetic shivering:**

Inj. Clonidine 3 microgram per kilogram administered intravenously inhibits or stops shivering mechanism is by inhibition of central thermoregulatory control.

**v) Attenuation of hemodynamic effects of ketamine:**

Oral Clonidine attenuates the heart rate and blood pressure increase that usually follows ketamine administration[21].

**vi) Diagnosis of phaeochromocytoma:**

Lack of suppression of plasma norepinephrine to less than 500 picogram / ml, 3 hours after a oral dose of 0.3mg Clonidine suggests phaeochromocytoma[15].

**vii) Treatment of diabetic diarrhoea.**

**viii) Treatment of hypertension :**

It is not used as a first line antihypertensive.

**ix) Induced hypotension:**

Clonidine is a useful adjunct in inducing deliberate Hypotension.

**ADVERSE EFFECTS :-**

Clonidine can cause bradycardia and hypotension. Sedation and dry mouth occur in 50% of cases. It may cause dryness of nose and eyes. It may sometimes cause parotid gland swelling and pain. Less common side effects like sleep disturbances with vivid dreams or nightmares, restlessness, depression and impotence may occur in some patients.

**CLONIDINE WITHDRAWAL PHENOMENA :-**

Sudden discontinuation of Clonidine results in headache, apprehension , tremors, abdominal pain, sweating , tachycardia and hypertension. It occurs usually 18-24 hours after stopping the drug. It occurs because of increased sympathetic discharge resulting in increased plasma and urinary catecholamine concentration. It is dose related , occurring rarely in patients taking a daily dose of Clonidine 0.3mg or less and more frequently and severely upon discontinuation of higher doses[15].

**DRUG INTERACTION:-**

1) Diuretics potentiate hypotension caused by clonidine.

2) Tricyclic antidepressants inhibit the antihypertensive effect of Clonidine by an

unknown mechanism.

**OVERDOSE :-**

It results in depression of sensorium, transient hypertension followed by hypotension and bradycardia. It may cause respiratory depression and miosis which resembles the effects of opioid overdosage.

In case of overdosage, ventilatory support and circulatory support with crystalloids, colloids, inotropic agents and atropine are needed.

**CONTRA-INDICATIONS:-**

Clonidine is contraindicated in patients with sinus node disease and atrioventricular node dysfunction. It is to be avoided in patients on diuretics having hemodynamic instability and in pregnant females. It should never be prescribed to a non-compliant patient who do not follow the instructions.

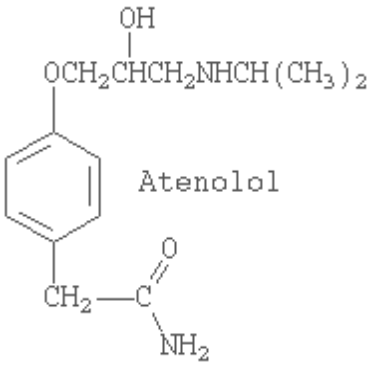
# PHARMACOLOGY OF ATENOLOL

Atenolol is a Beta (1)-selective (Cardio-selective) adreno-receptor antagonist.

## Chemical Name:

(RS)-4-(2-hyproxy 3-isopropylamino propoxy) phenylacetamide

## Structure:




($C_{14}$ $H_{22}$ $N_2$ $O_3$ )

## Physical properties:

It is a white, odourless powder. It has no intrinsic sympathomimetic activity or membrane – stabilizing activity[15].

| | |
|---|---|
| Melting point | 152-155 $^{0}$c |
| Dissociation constant | 9.6 @ 24 $^{0}$c |
| Partition co-efficient Log Kp* | 0.23 |

(* Log Kp – octanol: water partition co-efficient)

## Absorption, fate and excretion :

It is incompletely absorbed with only 50% oral bioavailability. But most of the absorbed drug reaches the systemic circulation (hydrophilicity). There is only little inter-individual variation in the plasma concentration of atenolol.

It crosses the Blood - Brain Barrier only to a limited extent and its peak effect is between 60- 120 minutes[15]. Atenolol is excreted largely unchanged in urine and the drug accumulates in patients with renal failure. It has an elimination half-life of 5-8 hours. The dosage should be reduced in patients with creatinine clearance of less than

35milliliters per minute**.**

## PHARMOCOLOGICAL ACTIONS:

### Effects of Beta-Blockade: -

Atenolol acts as a competitive inhibitor at beta-1 receptors, which are predominant in the heart. It has no marked effect on the normal heart in subjects at rest. But in the presence of increased sympathetic tone as with stress or exercise, the Beta-

Blockade in the heart prevents a rise in heart rate, cardiac output and stroke work. It results in reduction in myocardial contractility, suppression of automaticity and slowing down of atrio- ventricular conduction. The cardiac response to exercise and other stressful conditions in which sympathetic tone is increased is attenuated. Further, it decreases myocardial oxygen requirement and improves exercise tolerance in patients with angina.

**Activity as an antihypertensive agent:-**

Atenolol does not cause a reduction in blood pressure in patients with normal blood pressure[15]. It lowers blood pressure only in patients with Hypertension. The mechanism responsible for this important clinical effect is not well understood despite its wide spread use.

The release of renin from the juxta-glomerular apparatus is stimulated by the sympathetic nervous system and atenolol blocks this effect. Long-term administration of atenolol to hypertensive patients ultimately leads to a fall in peripheral vascular resistance. Though it has been hypothesized that the central actions of atenolol may also contribute to the antihypertensive effect, there is only little evidence available.

**Pulmonary system:**

Atenolol is less likely to increase airway resistance in patients with asthma. But, it has to be used with caution in patients with bronchospastic disease.

## Uses:

**1)Anti-hypertensive :**

Atenolol is used to reduce increased blood pressure. Initial dose is 50 mg/day once daily. If the patient does not respond after 3-4 weeks of therapy, the dose has to be increased to l00 mg/ day once daily.

**2)Anti-anginal:**

Atenolol relieves angina and improves exercise tolerance.

**3) Anti- arrhythmic**:

Atenolol is a class II anti-arrhythmic agent that helps to control the ventricular response rate in chronic Atrial fibrillation, Supraventricular tachycardia and in symptomatic premature ventricular complexes.

**4)** Atenolol reduces mortality and improves early survival in patients with myocardial infarction.

**5) In hyperthyroidism:**

Atenolol is effective in controlling sympathetic over activity. It controls the anxiety, tremor and tachycardia seen in these patients.

**6) Tremors:**

Though propranolol is the best choice, atenolol can be used to control essential tremors.

**7) Anxiety disorders:**

Atenolol reduces anxiety in patients with acute stress reactions, generalized anxiety disorders and panic disorder.

**8) Alcohol withdrawal:**

Atenolol is used as an adjunct to standard alcohol withdrawal treatments.

## Adverse effects:

The most frequent and serious side effect of Atenolol is because of its beta blockade.

1) **Cardio vascular system**: Atenolol may cause bradycardia, hypotension, heart block and congestive cardiac failure. Abrupt withdrawal of atenolol in chronically treated patients may precipitate angina and sudden death.

2) **Bronchospasm:** It can occur with Atenolol in susceptible patients.

3) **Central nervous system:** Atenolol may cause fatigue, depression, confusion, insomnia and nightmares.

4) **Gastrointestinal effects:** Atenolol can cause nausea, vomiting, diarrhoea, constipation and abdominal cramps.

5) **Raynaud's phenomenon:** Atenolol can worsen symptoms of peripheral vascular disease and may cause cold extremities

**PRECAUTIONS:**

1.Bronchospastic disorder:

Though cardio selective, atenolol should not be given to a patient with bronchospasm.

2. Diabetes Mellitus:

Atenolol blunts the recognition of hypoglycemia by patients with diabetes mellitus and is known as **hypoglycemia unawareness.**

3. Patients on long term treatment with atenolol:

Abrupt withdrawal of atenolol results in angina, myocardial infarction, ventricular arrhythmias and sudden death. Medication has to be discontinued gradually over a period of 1-2 weeks.

**OVERDOSAGE:**

Atenolol overdosage may cause hypotension, bradycardia, prolonged PR interval, widened QRS complex, seizures and depression.

**DRUG INTERACTION:**

i. Atenolol and calcium channel blockers have an additive effect on cardiac conduction system.
ii. Indomethacin and other non steroidal anti-inflammatory drugs can antagonize anti-hypertensive effect of atenolol.

# MATERIALS AND METHODS

Following local ethics committee approval, 75 ASA grade I or II patients of either sex aged from 20 to 60 years scheduled for various elective surgeries under general anaesthesia were included in the study. All of them required orotracheal intubation as part of their anaesthetic management and gave written informed consent to participate in the study.

Patients with cardiovascular disease, bronchospastic disease, cerebrovascular disease, peripheral vascular disease, hepatic and renal impairment, Diabetes mellitus, morbid obesity, anticipated difficult airway and those taking vasoactive drugs that are known to affect heart rate, blood pressure or hormonal stress responses were excluded from the study.

All patients were assessed preoperatively by history, physical examination, routine laboratory tests, chest X-ray and electrocardiogram. A preoperative visit was made to allay the anxiety and to develop a good rapport.

On the day of surgery , patients were examined in the waiting room and a base line pulse rate , blood pressure (systolic, diastolic and mean arterial pressure )

and respiratory rate were recorded. These values were noted down as the preoperative value **(PO).** Then the patients were randomly assigned into three groups of 25 patients each. Group I: control group patients received T.Diazepam 0.1mg/kg (rounded off to the nearest 5mg). Group II: clonidine group patients received T. Clonidine (CATAPRES) 5 microgram / kg, rounded off to the nearest 50 microgram (maximum 0.3 mg) in addition to T.Diazepam 0.1mg/kg rounded off to nearest 5 mg. Group III: Atenolol group patients received T.Atenolol 50 mg (TENORMIN) in addition to T. Diazepam 0.1mg/ kg rounded off to nearest 5 mg. All the drugs were given with sips of water about 2 hours prior to induction of anaesthesia . No anticholinergic drug was given either before or at the time of induction of anaesthesia.

In the waiting room, just before shifting the patients to operation theatre (2 hours after the study drug), an assessment of sedation and respiratory rate was done.

The degree of sedation was graded as follows

Sedation scoring[22]:

0 - patient awake and talkative

1 - patient awake but uncommunicative.

2 - patient drowsy, quiet and easily arousable.

3 - patient asleep.

On arrival in the operating room a 18 gauge intravenous cannula was placed and crystalloid was started . Patients were monitored with a non-invasive monitor throughout the study period. Monitored parameters include heart rate, blood pressure ( systolic, diastolic and mean arterial pressure ) , oxygen saturation and electrocardiogram.

After a stabilization period of 3 minutes a baseline heart rate, blood pressure (systolic, diastolic and mean arterial pressure) were recorded. These values were noted down as preinduction values **(PI).** All the patients were preoxygenated with 100% oxygen for 3 minutes. Patients were induced with Inj. Thiopentone sodium 2.5% - 5 mg / kg intravenously followed by Inj. Succinylcholine 1.5 mg/ kg body weight. A digital stopwatch was used to time the events.

Heart rate and blood pressure ( systolic, diastolic and mean arterial pressure ) were recorded during laryngoscopy and endotracheal intubation (**LI**) and thereafter at one, three and five minutes after intubation ( **I-1, I-3 and I-5** respectively).

All patients were intubated with appropriate size cuffed, portex endotracheal tube.

Any patients who strained or took more than 15 seconds of laryngoscopy or required a second attempt of laryngoscopy and intubation were excluded from the

study.

All patients were ventilated using $O_2$ : $N_2O$ = 40% :60%, inj. Vecuronium 0.08 mg per kg without any addition of narcotic or volatile anaesthetic agent. No surgical stimulation was allowed for five minutes after intubation.

Intraoperatively, patients were observed for side effects like hypotension, bradycardia, hypertension, tachycardia and arrhythmias.

Inj. Pentazocine 0.6 mg/kg was given intravenously after the observation period (5 minutes after intubation). After completion of surgery, neuromuscular blockade was reversed with Inj. Neostigmine 0.04 mg/kg and Inj. Atropine 0.02 mg/kg intravenously. Patients were extubated after thorough suctioning and shifted to postoperative ward. Any delay in recovery was noted.

Patients were observed for complications like hypotension, bradycardia, hypertension, tachycardia, vomiting, shivering in the postoperative ward. They were observed every 1-hour up to 12 hours and thereafter every 2 hours up to 24 hours.

Results were systematically analysed by 't'-test to find out the significance between the groups and in the groups at different periods of study from the preoperative basal value. A p-value of less than 0.05 was considered as statistically significant.

# OBSERVATION AND RESULTS

The mean age and mean weight of the patients in all the three groups were comparable. The number of males (9) and females (16) were equal in all the three groups.

**TABLE - I: DEMOGRAPHIC DATA**

| PARAMETERS | CONTROL GROUP | CLONIDINE GROUP | ATENOLOL GROUP |
|---|---|---|---|
| **AGE (YEARS)** | | | |
| MEAN | **33.64** | **34.88** | **35.32** |
| RANGE | **18 - 60** | **21 -60** | **20 -59** |
| **SEX** | | | |
| MALE | **9** | **9** | **9** |
| FEMALE | **16** | **16** | **16** |
| **BODY WEIGHT (KG)** | | | |
| MEAN | **52.4** | **53.56** | **54.76** |
| RANGE | **40 - 61** | **44 - 70** | **46 - 62** |

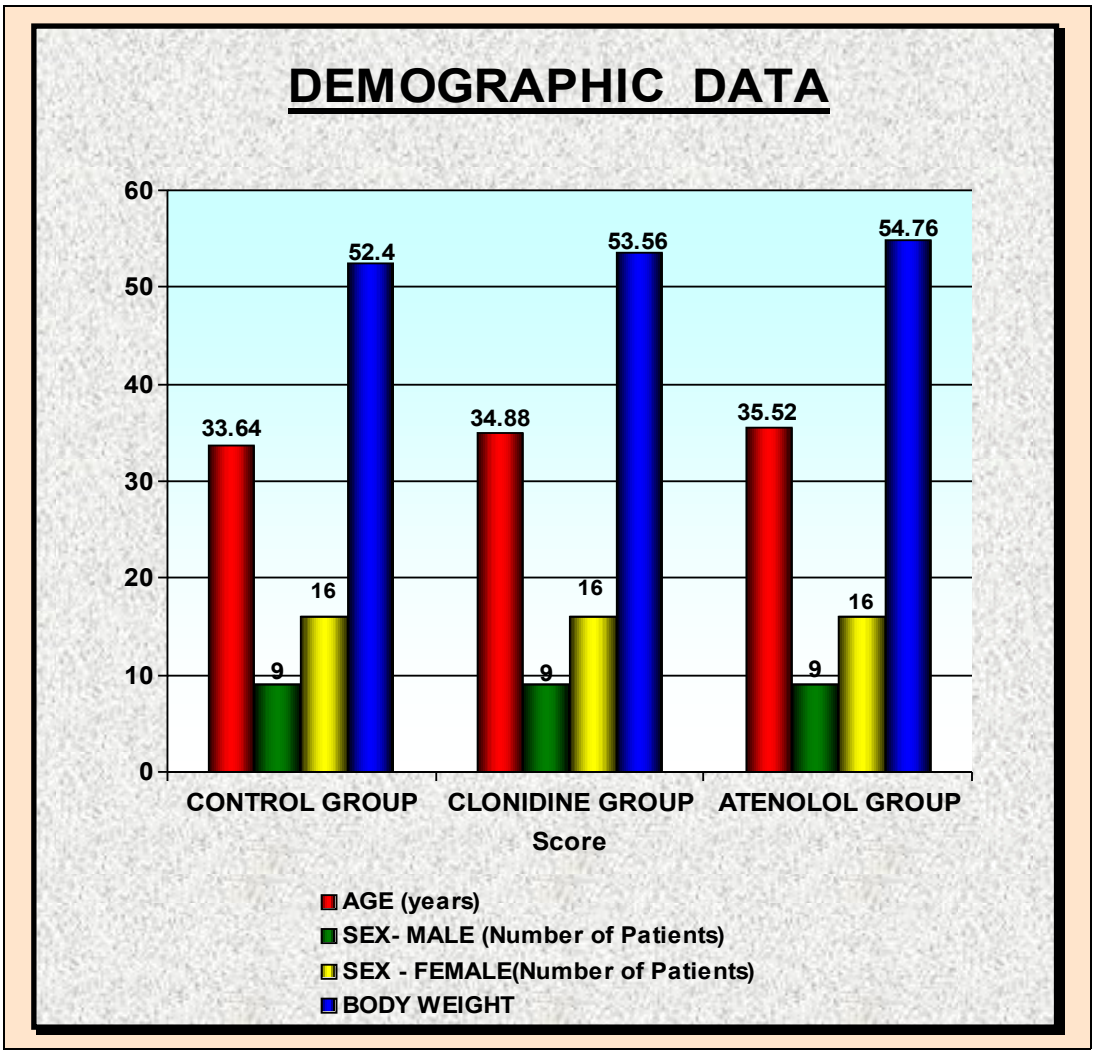

DEMOGRAPHIC DATA
60
50
40
30
20
10
0
33.64
9
16
52.4
34.88
9
16
53.56
35.52
9
16
54.76
CONTROL GROUP
CLONIDINE GROUP
ATENOLOL GROUP
Score
AGE (years)
SEX- MALE (Number of Patients)
SEX - FEMALE(Number of Patients)
BODY WEIGHT

**TABLE II: SEDATION SCORING IN DIFFERENT GROUPS**

| GROUPS | SEDATION SCORE | | | |
|---|---|---|---|---|
| | 0 | 1 | 2 | 3 |
| CONTROL | 15 (60%) | 8 (32%) | 1 (4%) | 1 (4%) |
| CLONIDINE | 2 (8%) | 3 (12%) | 10 (40%) | 10 (40%) |
| ATENOLOL | 16 (64%) | 8 (32%) | 1 (4%) | 0 (0%) |

Clonidine provided better sedation ( 80% of patients in sedation score 2-3 ) when compared to control and atenolol group ( 60% of patients remaining awake) . There was no significant difference in sedation between control and Clonidine group.

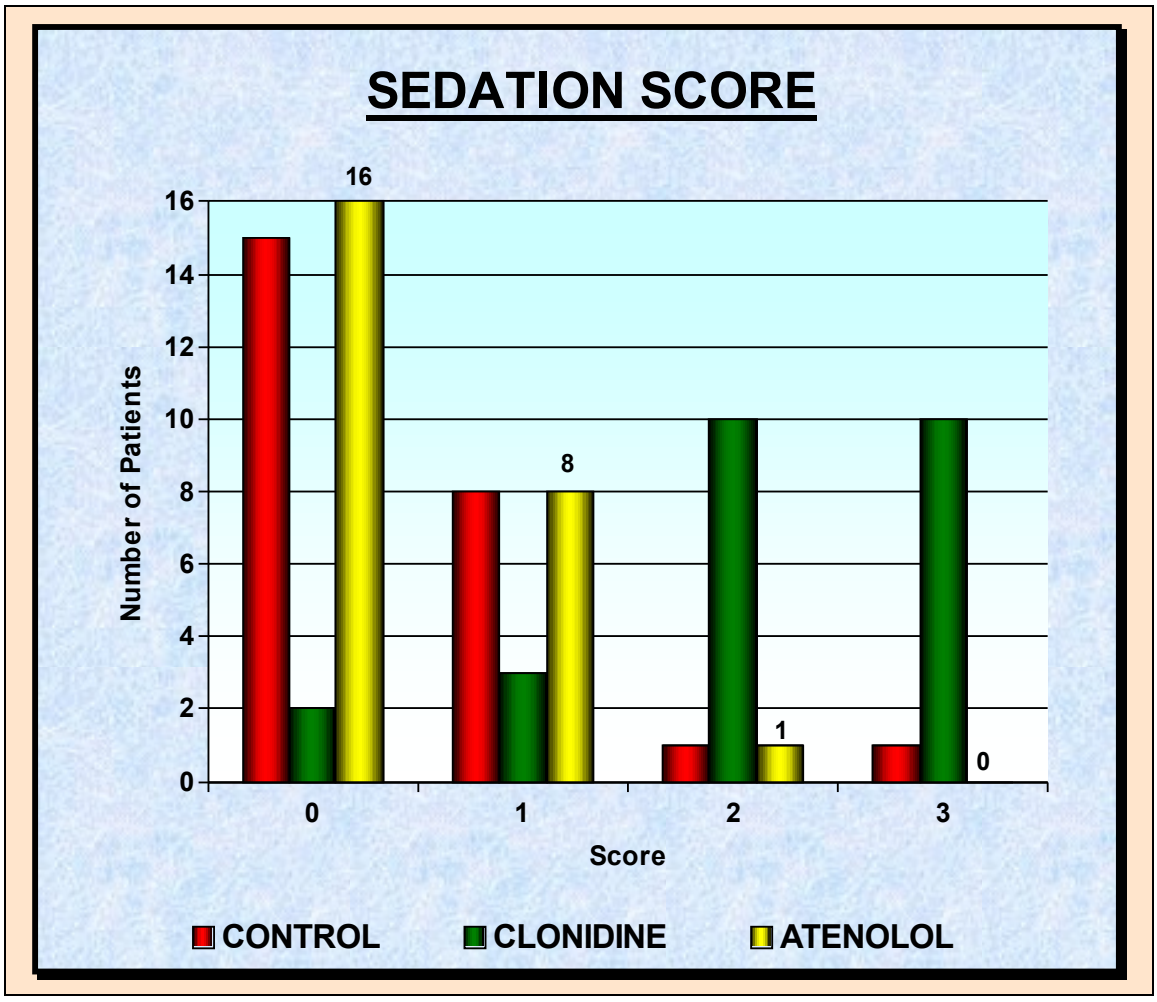

SEDATION SCORE
16
8
1
0
16
14
12
10
8
6
4
2
0
Number of Patients
0
1
2
3
Score
CONTROL
CLONIDINE
ATENOLOL

**TABLE III: CHANGES IN HEART RATE (MEAN ± STANDARD DEVIATION BEATS PER MINUTE ) IN ALL THE THREE GROUPS COMPARED WITH THEIR RESPECTIVE PREOPERATIVE VALUES AT DIFFERENT TIME INTERVALS.**

| TABLE III: | | | |
|---|---|---|---|
| HEART RATE (MEAN ± S.D) IN BEATS PER MINUTE | | | |
| TIME | GROUPS | | |
| | CONTROL | CLONIDINE | ATENOLOL |
| PO | 80.88 ± 6.98 | 81.84 ± 5.68 | 80.8 ± 5.09 |
| PI | 91.64 ± 7.17 | 74.76 ± 3.503 | 75.44 ± 4.27 |
| LI | 112.8 ± 7.08 | 87.28 ± 3.13 | 87.2 ± 4.66 |
| I-1 | 115.24 ± 6.35 | 84.68 ± 3.997 | 89.96 ± 3.96 |
| I-3 | 103.68 ± 4.375 | 73.92 ± 3.818 | 84.08 ± 4.28 |
| I-5 | 96.56 ± 4.375 | 72.28 ± 2.89 | 79.36 ± 4.03 |

In the preoperative period, before giving the premedication the mean heart rate in all the three groups were comparable as in

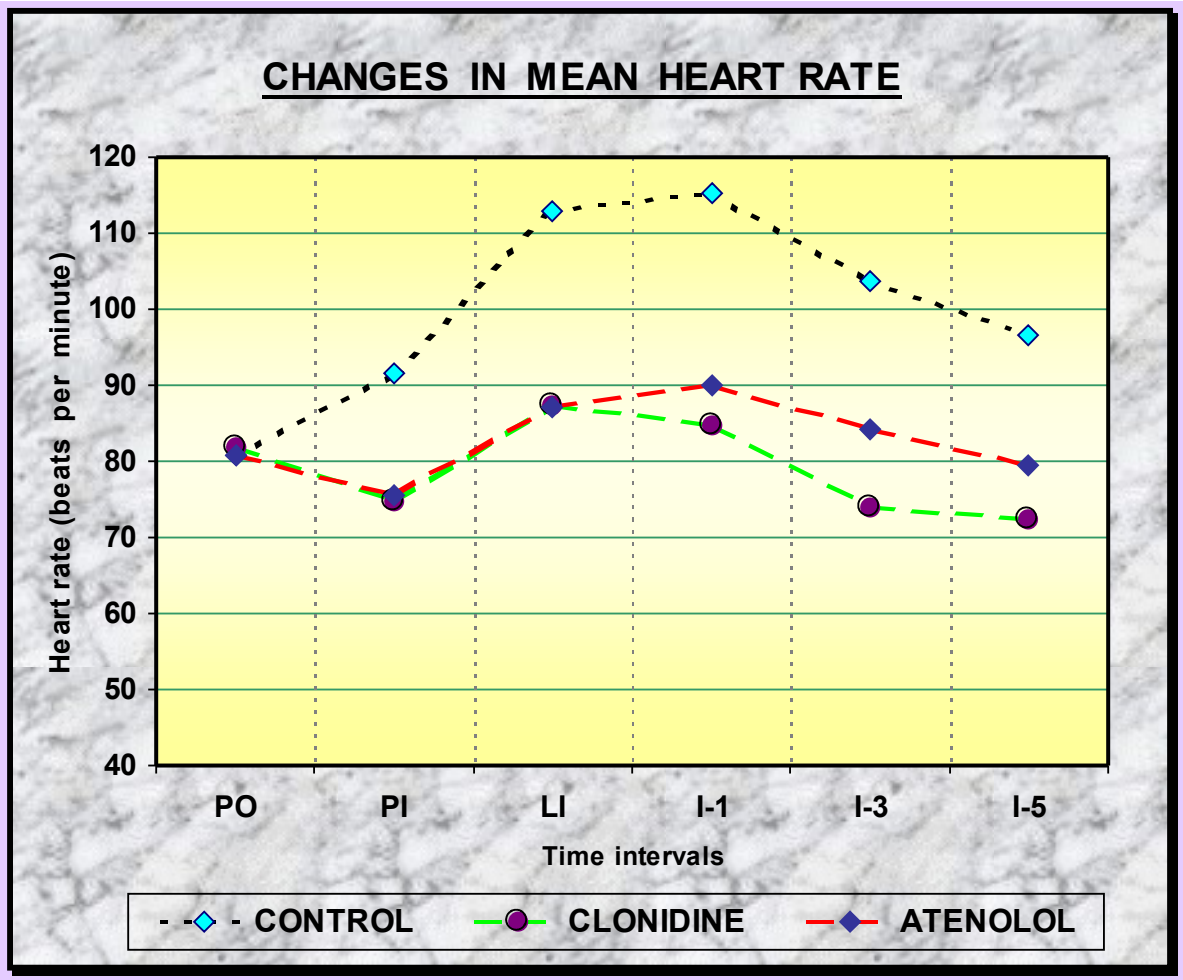



**TABLE III**. Before induction of anaesthesia, 90 – 120 minutes after premedication, the heart rate( mean ± S.D) significantly decreased from the preoperative value in clonidine and atenolol group ($p<0.05$) whereas it was significantly increased in the control group ($p<0.05$) **(TABLE III).** During this period, the decrease in heart rate from 81.84 ±5.68 and 80.8±5.09 to

74.76±3.503 and 75.44±4.27 respectively in the clonidine and atenolol group was significant when compared to the increase in heart rate from 80.88 ±6.98 to 91.64±7.17 in control group ($p < 0.05$) but there was no significant difference between clonidine and atenolol group ($p > 0.05$).

During direct laryngoscopy and endotracheal intubation, there was significant increase in heart rate (mean ± S.D ) from their respective preoperative values in all the three groups ( $p < 0.05$). However, the increase in heart rate (mean ± S.D ) was significantly lower in the clonidine and atenolol group when compared to the control group (increased by 30% in control group , by 6% in clonidine group, by 10% in the atenolol group, **$p<0.05$)** but there was no significant difference between clonidine and atenolol group **($p>0.05$).**

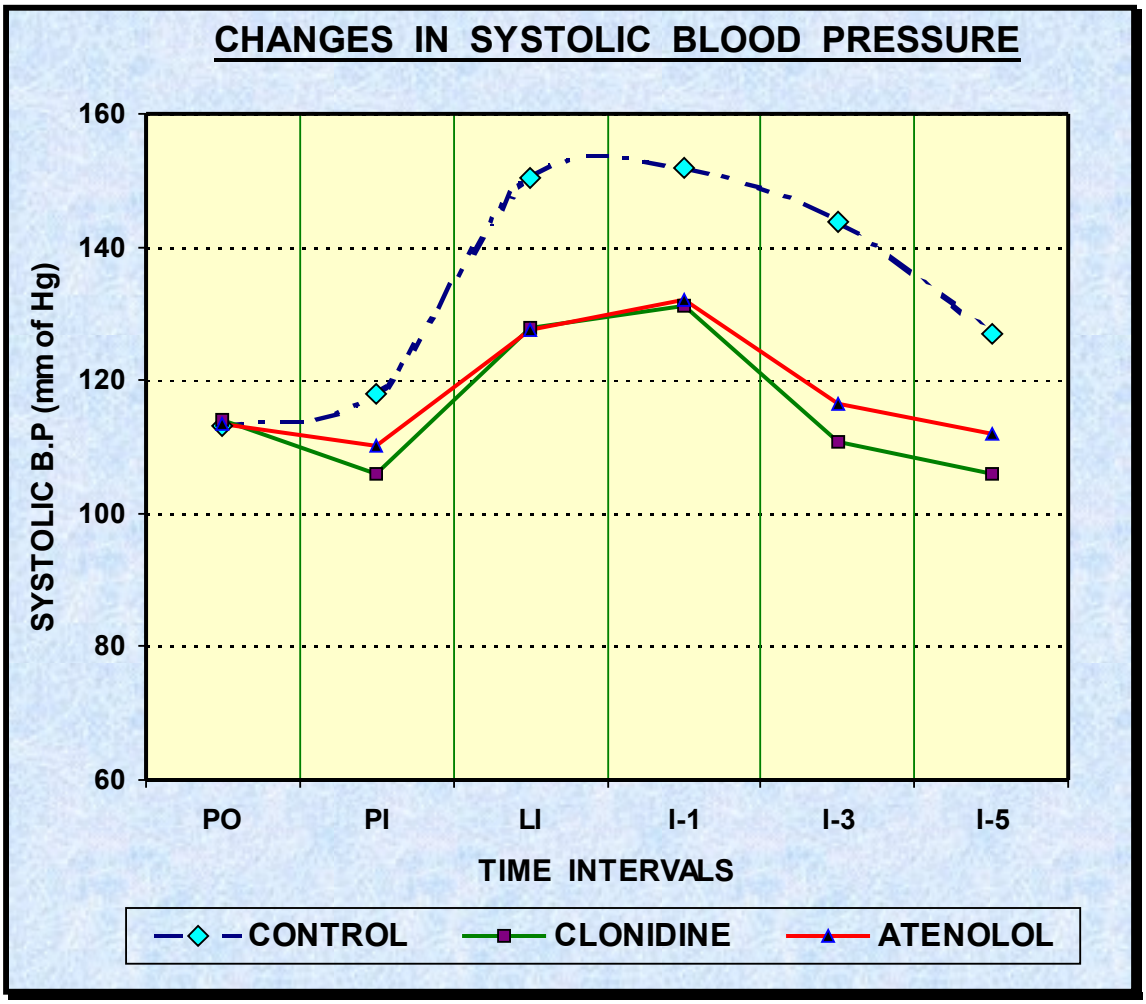
The heart rate (mean ± S.D) returned to preoperative value at one minute after intubation in the clonidine group, at five minutes after intubation in the atenolol group whereas in the control group it remained significantly higher at five minutes after intubation.

After intubation, during the observation period of five minutes , the decrease in heart rate in atenolol group was significantly less than the Clonidine group ( $p < 0.05$) but was significantly more than the control group ( $p < 0.05$).

The systolic blood pressure in the preoperative period was comparable in all the three groups (**TABLE IV**). During the preinduction period, 2 hours after premedication, the blood pressure increased significantly in the control group ($p<0.05$) but it decreased in the clonidine group ($p<0.05$) and atenolol group ($p>0.05$).

**TABLE IV: CHANGES IN SYSTOLIC BLOOD PRESSURE (MEAN ± STANDARD DEVIATION mm of Hg) IN ALL THE THREE GROUPS COMPARED WITH THEIR RESPECTIVE PREOPERATIVE VALUES AT DIFFERENT TIME INTERVALS.**

| TABLE IV: | | | |
|---|---|---|---|
| SYSTOLIC BLOOD PRESSURE (MEAN ± S.D) IN mm of Hg | | | |
| TIME | GROUPS | | |
| | CONTROL | CLONIDINE | ATENOLOL |
| PO | 113.04 ± 9.697 | 114.16 ± 7.636 | 113.36 ± 9.604 |
| PI | 118.08 ± 8.154 | 105.84 ± 4.47 | 110.08 ± 8.376 |
| LI | 150.44 ± 9.39 | 127.8 ± 5.902 | 127.68 ± 6.414 |
| I-1 | 152 ± 9.63 | 131.28 ± 5.35 | 131.96 ± 5.93 |
| I-3 | 143.68± 8.86 | 110.72 ± 6.23 | 116.52 ± 7.611 |
| I-5 | 127.04 ± 6.88 | 105.8 ± 5.21 | 112 ± 7.49 |




During laryngoscopy, endotracheal intubation and at one minute after intubation, the systolic blood pressure increased in all the three groups but the increase was significantly less in the clonidine group and atenolol group when compared with the control group (increased by 26% in control group vs. 13% in clonidine group

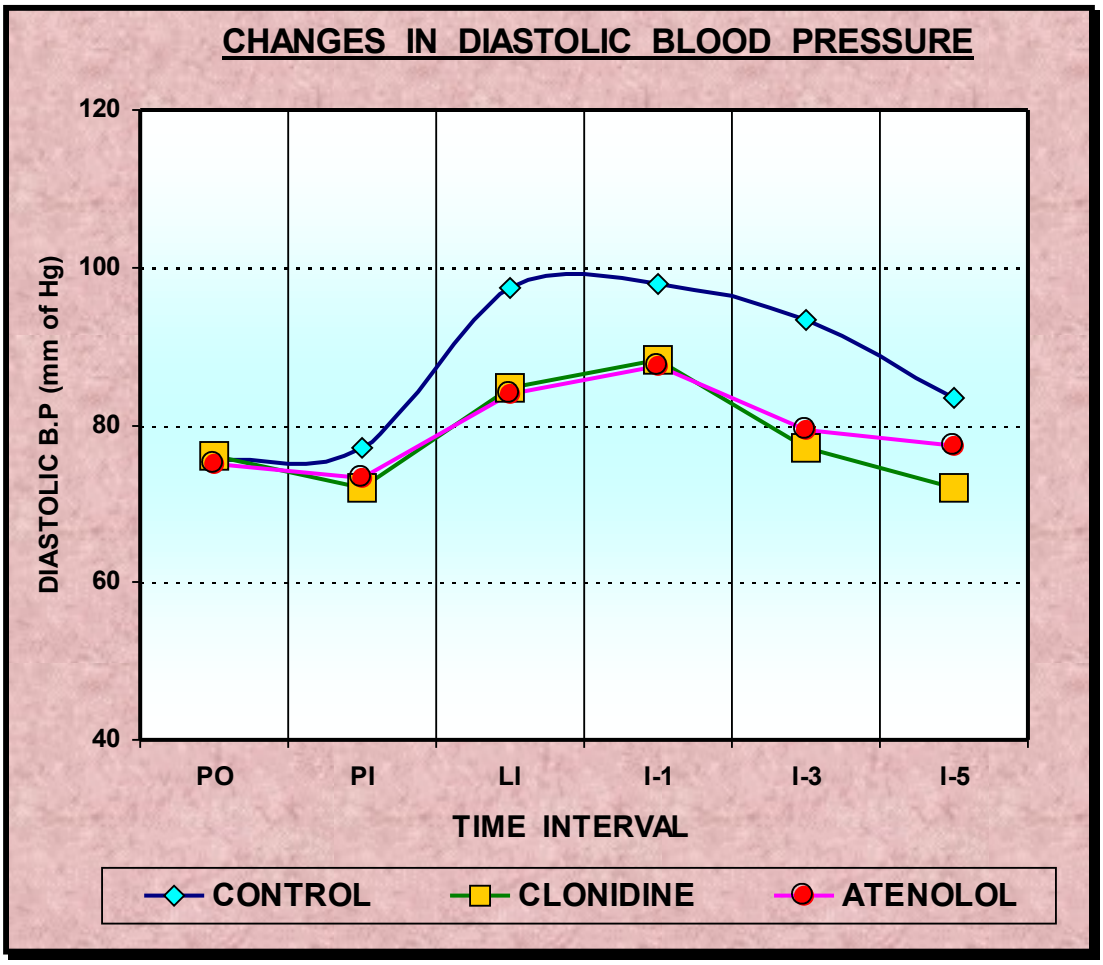
and 14% in atenolol group, $p<0.05$) .

The raised systolic blood pressure returned to preoperative level at three minutes after intubation in the clonidine group, at five minutes after intubation in the atenolol group whereas in the control group, it did not return to the preoperative level at five minutes after intubation.

During the preoperative period, the diastolic blood pressure was comparable in all the three groups ( **TABLE V**). During the preinduction period, the diastolic pressure decreased from the preoperative values in clonidine group ($p<0.05$) and atenolol group ($p>0.05$) whereas the diastolic pressure increased in the control group ($p>0.05$).

**TABLE V: CHANGES IN DIASTOLIC BLOOD PRESSURE (MEAN ± STANDARD DEVIATION mm of Hg) IN ALL THE THREE GROUPS COMPARED WITH THEIR RESPECTIVE PREOPERATIVE VALUES AT DIFFERENT TIME INTERVALS.**

| TABLE V: | | | |
|---|---|---|---|
| DIASTOLIC BLOOD PRESSURE (MEAN ± S.D) IN mm of Hg | | | |
| TIME | GROUPS | | |
| | CONTROL | CLONIDINE | ATENOLOL |
| PO | 75.68 ± 5.186 | 76 ± 4.397 | 75.12 ± 4.4 |
| PI | 77.2 ± 2.944 | 72.08 ± 3.26 | 73.28 ± 4.505 |
| LI | 97.48 ± 4.805 | 84.76 ± 2.21 | 83.84 ± 4.26 |
| I-1 | 97.84 ± 3.77 | 88.28 ± 2.303 | 87.44 ± 4.17 |
| I-3 | 93.32 ± 4.12 | 77.16 ± 2.48 | 79.4 ± 3.89 |
| I-5 | 83.4 ± 3.71 | 72.04 ± 3.129 | 77.44 ± 4.05 |




During laryngoscopy, endotracheal intubation and at one minute after intubation, the diastolic blood pressure increased in all the three groups but the increase was significantly less in the clonidine group and atenolol group when compared with the control group (increased by 23% in control group vs. 14% in clonidine group and 14% in atenolol group, $p<0.05$) .

The raised distolic blood pressure returned to preoperative level at three minutes after intubation in the clonidine group, at five minutes after intubation in the atenolol group whereas in the control group, it did not return to the preoperative level at five minutes after intubation.

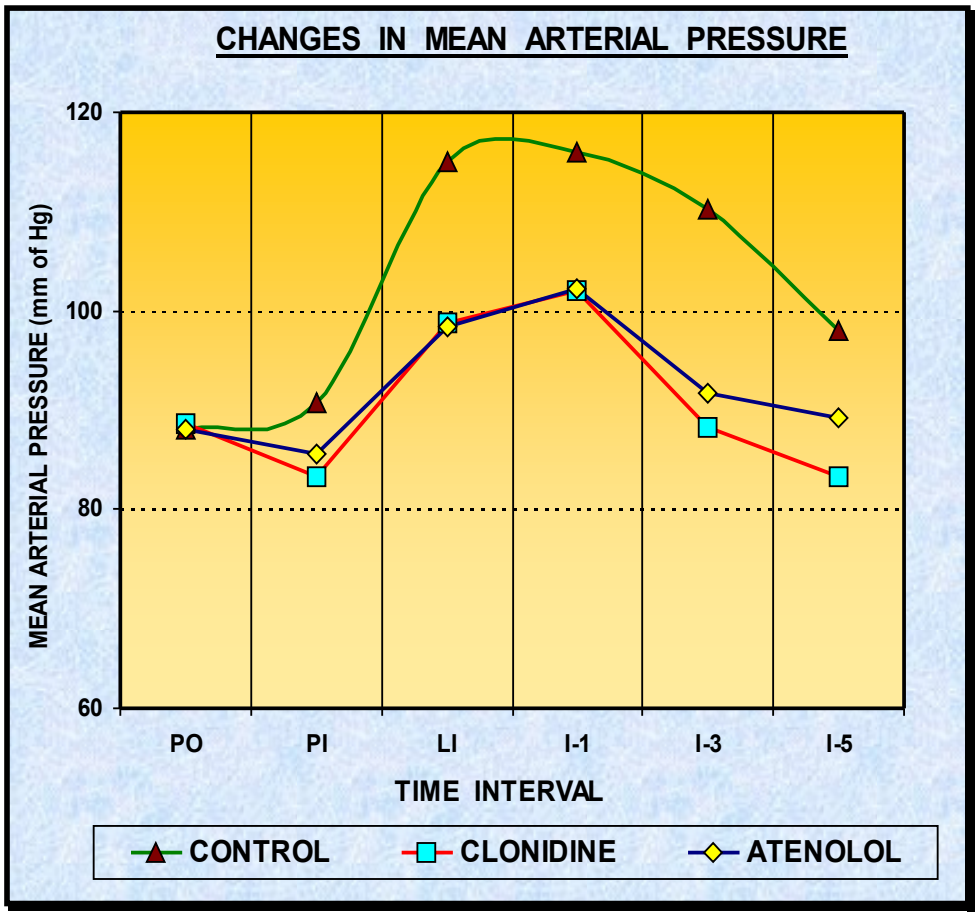
During the preoperative period, the mean arterial pressure was comparable in all the three groups ( **TABLE VI**).

During the preinduction period, the mean arterial pressure decreased from the preoperative values in clonidine group ($p<0.05$) and atenolol group ($p>0.05$) whereas the mean arterial pressure increased in the control group ($p>0.05$). During

laryngoscopy, endotracheal intubation and at one minute after intubation, the mean arteial pressure increased in all the three groups but the increase in clonidine group and atenolol group was significantly

**TABLE VI: CHANGES IN MEAN ARTERIAL PRESSURE (MEAN ± STANDARD DEVIATION mm of Hg) IN ALL THE THREE GROUPS COMPARED WITH THEIR RESPECTIVE PREOPERATIVE VALUES AT DIFFERENT TIME INTERVALS.**

| TABLE VI: | | | |
|---|---|---|---|
| MEAN ARTERIAL PRESSURE (MEAN ± S.D) IN mm of Hg | | | |
| TIME | GROUPS | | |
| | CONTROL | CLONIDINE | ATENOLOL |
| PO | 88.04 ± 6.08 | 88.68 ± 4.12 | 88.16 ± 5.93 |
| PI | 90.84 ± 3.91 | 83.4 ± 2.94 | 85.52 ± 4.66 |
| LI | 115.12 ± 5.64 | 98.76 ± 2.934 | 98.32 ± 4.29 |
| I-1 | 115.96 ± 4.93 | 102 ± 2.5 | 102.24 ± 4.26 |
| I-3 | 110.28 ± 4.89 | 88.28 ± 3.23 | 91.76 ± 4.32 |
| I-5 | 98 ± 3.67 | 83.24 ± 3.07 | 89.2 ± 4.5 |


CHANGES IN MEAN ARTERIAL PRESSURE
120
100
80
60
MEAN ARTERIAL PRESSURE (mm of Hg)
PO
PI
LI
I-1
I-3
I-5
TIME INTERVAL
CONTROL
CLONIDINE
ATENOLOL

less when compared to control group (increased by 24% in control group vs. 13% in clonidine group and 14% in atenolol group, $p<0.05$) .

The raised mean arterial pressure returned to preoperative level at three minutes after intubation in the clonidine group, at five minutes after intubation in the atenolol group whereas in the control group, it did not return to the preoperative level at five minutes after intubation **(TABLE VI).**

**TABLE VII shows changes in respiratory rate 90 –120 minutes after premedication. After premedication, there was no significant change in the respiratory rate in any of the groups ($p>0.05$).**

**TABLE VII: CHANGES IN RESPIRATORY RATES IN DIFFERENT GROUPS.**

| TABLE VII | RESPIRATORY RATE (BREATHS PER MINUTE) | |
|---|---|---|
| GROUP | BEFORE PREMEDICATION | 120 MINUTES AFTER PREMEDICATION |
| CONTROL | 14.88 ± 1.364 | 15.12 ± 1.299 |
| CLONIDINE | 15.04 ± 1.24 | 15 ± 0.96 |
| ATENOLOL | 15.08 ± 1.19 | 15.12 ± 1.17 |

# REVIEW OF LITERATURE

The hemodynamic consequences of endotracheal intubation have been the subject of study by various authors over many years.

**Ried and Brace (1940)** postulated that the reflex circulatory responses to laryngeal instrumentation were mediated through the vagus nerve and named it as "**VASOVAGAL REFLEXES.**"

**King et al (1951)**[23] observed that a marked though, transient rise in blood pressure is often encountered during laryngoscopy and manipulation of the epiglottis.

They also believed that the reflex mechanism to be non-specific. They stated that the impulses initiating the reflex are probably carried by the vagus nerve while the effector system is less clearly defined and may be due to decreased parasympathetic or increased sympathetic activity.

**Prof. ward and king (1960)** in their study documented myocardial ischemic changes due to reflex sympathoadrenal response following larygoscopy and intubation with mean increase in the systemic pressure of 40 mm of Hg even in normotensive individuals.

**Tomori et al (1969)**[12] in their study observed that mechanical stimulation of four

areas of the respiratory tract, the nose, the epipharynx, the laryngopharynx and tracheobronchial tree induced reflex cardiovascular responses associated with enhanced neuronal activity in cervical sympathetic efferent fibres. It was more pronounced during stimulation of the epipharynx.

**Corbett and kerr (1969)**[24] found a significant increase in mean arterial pressure and plasma nor-adrenaline levels one minute after intubation that gradually regressed with time. No significant changes in Adrenaline and Dopamine concentration were noted during the same period.

**Forbes and Dally (1970)**[25] observed an increase in mean arterial pressure of 25 mmHg in all 22 normotensive patients during laryngoscopy and endotracheal intubation. These response were interpreted as due to reflex sympathetic adrenal stimulation.

**Prys-Roberts et al (1971)**[2] observed that increases in heart rate and blood pressure during laryngoscopy and intubation were much more exaggerated in hypertensive patients than in normotensives.

**Victoria Faria Baln and Normand A.G.(1974)** in the article, complications of tracheal intubation have classified the neurogenic or reflex mediated complication into three different categories.

i. Laryngeal reflexes:

Spasm of glottis, bronchospasm, apnoea, bradycardia, dysrhythmia and hypotension can occur.

The mere presence of the tracheal tube seem to be the most common cause of bronchospasm in anaesthetized asthmatic patients.

ii. Laryngo-sympathetic reflexes:

Tachydysrhythmia, acute arterial hypertension and a hyperdynamic state can occur. It is related to an increased nor-adrenaline function of the total catecholomine.

iii. Laryngospinal reflexes:

coughing, vomiting and bucking may occur

**Stoelting (1978)**[3] recommended that attempt should be made to attenuate the pressor response of laryngoscopy and tracheal intubation when the laryngoscopy time is likely to be more than 30 seconds. when laryngoscopy is prolonged laryngotracheal rather than intravenous lidocaine is necessary for attenuating the circulatory responses to intubation.

**Stoelting et al (1979)**[6] studied the effect of sodium nitroprusside

1 mcg/kg vs. 2 mcg/kg administered 15 seconds before performing laryngoscopy and stated that 2 microgram per kilogram was more effective in attenuating the pressor response associated with laryngoscopy and intubation.

**Safawat et al (1981)**[8] studied the effect of propranolol 0.5 -1 mg administered intravenously 4 minutes before laryngoscopy in patients undergoing coronary artery bypass grafting. They found that in patients treated with propranolol there was a marked cardiovascular stability after intubation.

**Kautto et al (1982)**[4] observed that fentanyl in a low dose of 2 mcg / kg attenuated the pressor response to intubation.

**Black et al (1984)**[5] compared the efficacy of Alfentanil with fentanyl. He observed Alfentanil to be effective in attenuating the hemodynamic response to larygoscopy and intubation and the effect appears to be of shorter duration than that of fentanyl.

**Ghignone et al (1987)**[26] observed that clonidine 5 mcg/ kg administered to patients with hypertension (blood pressure from normal to moderate) was more effective in blunting the reflex tachycardia associatiated with largygoscopy and intubation than lidocaine –fentanyl pretreatment.

**Pouttu et al (1987)**[27] evaluated the effect of clonidine (4.5 mcg /kg) on stress response during general anaesthesia in 21 female patients undergoing breast surgery

they observed that clonidine attenuated the sympathoadrenal response and the increase in heart rate and arterial blood pressure were lower in that group.

**Ghignone et al (1988)**[28] further studied the effect of clonidine on intraocular pressure in elderly patients undergoing ophthalmic surgery. He observed that in patients on clonidine who were managed with general anaesthesia, rise in intraocular pressure was prevented and further the cardiovascular responses associated with largygoscopy and intubation were attenuated. They have recommended clonidine as a useful adjunct in the management of elderly patients coming for ophthalmic surgery.

**Stone et al (1988)**[29] in a non-double blind prospective randomized study, examined the electrocardiograms of 128 mildly hypertensive patients in order to determine the incidence of myocardial ischemia during anaesthesia. They observed the patients who were not on chronic antihypertensives but who had received a small dose of a beta blocker (Atenolol. Lebetolol or Oxprenolol) along with premedication showed significantly reduced incidence ($p<0.001$) of myocardial ischemia.

**Nishikawa et al (1991)**[10] studied about premedication with oral Clonidine in a dose of 5 mcg / kg and observed that it could attenuate the pressor response associated with larygoscopy and tracheal intubation.

**Helfman et al (1991)**[30] compared Lidocaine, Fentanyl and Esmolol in attenuating the hemodynamic response to laryngoscopy and tracheal intubation. Similar study was done by **Feng et al (1996)**[31]**.** In both the studies they have concluded that only Esmolol, a cardioselective beta-blocker offered a consistent and reliable protection in attenuating both tachycardia and hypertension associated with tracheal intubation.

**Chadha et al (1992)**[32] evaluated oral clonidine pretreatment for homodynamic stability during craniotomy. They observed that pressor response to larygoscopy, tracheal intubation and skin infiltration was significantly attenuated in the clonidine group. Further they have observed a reduction in sleep dose of thiopentone sodium in clonidine pretreated patients.

**Dorman et al (1993)**[33] observed that clonidine (5 mcg /kg ) improves perioperative myocardial ischemia in patients undergoing Coronary Artery Bypass Surgery. **Yin et al (2002)** observed the same results in coronary artery disease patients undergoing non-cardiac surgery.

**Stuhmeier et al (1996)**[34] studied the effect of small dose of clonidine (2 mcg / kg ) in patients undergoing vascular surgery and observed that it reduces the incidence of myocardial ischemia.

**Thomson et al (1998)**[17] compared clonidine with conventional preanaesthetic medication (Morphine with Scopolamine or Lorazepam ) in patients undergoing CABG and observed that clonidine produces sedation, relieves anxiety as effective as conventional premedicant. They also observed that clonidine significantly reduced the isoflurane requirements.

**Tetsu kimura et al (1998)**[35] observed that premedication with oral clonidine (5 mcg/kg ) attenuated the initial increase in heart rate without subsequent decrease in heart rate after intravenous Neostigmine – Atropine administration. .

**Grundmann et al (1997)**[36] observed the intraoperative administration of 2 mcg/kg of clonidine is suitable for prevention of postanaesthetic shivering without prolonging the recovery time.

**Michael A.Campagni et al (1999)**[37] evaluated oral clonidine and intravenous esmolol regarding hemodynamic changes associated with injection of an epinephrine containing local anaesthetic solution during endoscopic sinus or septoplasty surgery in young healthy non smokers. They observed that Tablet clonidine 0.2-0.4 mg was efficient in blunting the hemodynamic response.

**Handa et al (2000)**[21] conducted a randomized double blind, placebo controlled study to determine the effect of oral clonidine premedication on the side effects of intravenous ketamine anaestheia. They observed that oral clonidine 5 mcg /kg attenuated the cardiostimulatory effects and was associated with reduced incidence and severity of nightmare and salivation attributable to intravenous ketamine.

**Eva oddby – muhrbeck et al (2002)**[38] observed that co-induction with clonidine significantly increased the number of Postoperative nausea & vomiting (PONV) free patients after breast cancer surgery with General anaesthesia.

**Dipak L. Raval et al (2002)**[22] conducted a study to compare the effectiveness of oral clonidine ( 4 microgram per kilogram) as a premedicant and also for attenuation of hemodynamic response to laryngoscopy and endotracheal intubation with oral diazepam and placebo. Clonidine provided extra advandage over diazepam and placebo by blunting hemodynamic response during laryngoscopy and endotracheal intubation and also by its antisialogogue effect.

**Javaid A.Zargar et al (2002)**[9] conducted a comparative study of the effect of metoprolol and esmolol on rate pressure product and ECG changes during laryngoscopy and endotracheal intubation in controlled hypertensive patients. They have concluded that esmolol in a bolus dose of 25 mg before induction of anaesthesia was comparatively better than metoprolol in attenuating the hemodynamic responses to laryngoscopy and endotracheal intubation like rate pressure product and ECG changes.

# DISCUSSION

Reflex tachycardia and hypertension during laryngoscopy and tracheal intubation occurs frequently, even in rightly anaesthetized normotensive individuals[39].

Several drugs and techniques have been tried in an attempt to obtund the hyperactive sympathoadrenal pressor response to laryngoscopy and intubation. In our study we have compared the efficacy of oral Clonidine ( 5 micrograms per kilogram) and oral Atenolol (50 milligram single dose) in attenuating the hemodynamic response to laryngoscopy and endotracheal intubation. 75 patients were studied with each group comprising 25 patients.

In our study, the patients in the Clonidine group were better sedated (80% of patients with sedation score 2-3 ) when compared to control group (64% patients fully awake) and Atenolol group ( 60% of patients fully awake). Kumar et al[40] and Ghignone et al[28] have also reported Clonidine as a better sedative when compared to Diazepam in their study.

In our study, 120 minutes after premedication , there was a small but significant fall in heart rate (from 81.84 ± 5.684 to 74.76±3.503 ) and blood pressure in the clonidine group. Kumar et al[40] and Ghignone et al[28] also observed the same

with oral Clonidine premedication..

In Atenolol group, 120 minutes after premedication, there was significant reduction in heart rate (from 80.8 ± 5.09 to 75.44 ± 4.273 ) but the decrease in the blood pressure was not significant. Atenolol probably by its beta-1 adrenoreceptor blockade, slows the conduction of cardiac impulses and decreases the heart rate. The blood pressure does not decrease significantly probably because Atenolol does not lower blood pressure in normotensive individuals[15] .

Laurito et al[41] has suggested that oral Clonidine, as a premedicant in a dosage of 5 micrograms per kilogram ( maximum 0.3 milligram)
affords hemodynamic protection to patients undergoing a
15 second laryngoscopy but not for patients undergoing a 45 second laryngoscopy. In our study, we have used the same dosage of
oral clonidine and we have limited our laryngoscopy time to less than 15 seconds.

During laryngoscopy and intubation, the heart rate increased in all the groups from their respective preoperative values ( increased by 30% in control group , by 6% in Clonidine group, by 10% in the Atenolol group). But, the increase in heart rate in Clonidine group and Atenolol group was not as much as that of in control group .

During laryngoscopy and intubation, the blood pressure (systolic, diastolic and mean arterial pressure) increased in all the three groups (mean arterial pressure increased by 30.76% in control group, 11% in Clonidine group, 11.5% in Atenolol group). The magnititude of increase in blood pressure in the Clonidine and Atenolol groups was similar and the increase was significantly less when compared to control group. Nishikawa et al[10], Pouttu et al[27] and Batra et al[42] obtained similar results when using oral Clonidine as a premedicant.

Clonidine minimizes the increase in heart rate and blood pressure during laryngoscopy and intubation by a complex mechanism. Centrally, it acts on the alpha-2 adrenoreceptors and causes decrease in central sympathetic tone and an increase in the parasympathetic tone. Peripherally, stimulation of alpha-2 adrenoreceptors leads to diminished release of noradrenaline from the nerve endings to the vasculature and a reduction in peripheral sympathetic tone. Beta adrenoreceptor blockade minimizes increase in heart rate and myocardial contractility by attenuating the positive inotropic and chronotropic effects of increased adrenergic activity. Atenolol, because of its selective beta adrenergic antagonistic activity like Metoprolol and Esmolol, is used to prevent the reflex sympathoadrenal discharge mediated tachycardia and hypertension during procedures of laryngoscopy and endotracheal intubation[9]. In our study, in the

control group, sinus tachycardia occurred in most of the patients whereas no patients in the Clonidine group and Atenolol group had any arrhythmias. In all the three groups, no patient had ECG changes suggestive of myocardial ischemia.

Oral Clonidine premedication was associated with a significant decrease in the incidence of postoperative nausea and vomiting in our study (12% in Clonidine group vs. 40% in control group and 36% in Atenolol group). Antiemetic property of Clonidine may be due to its action on alpha-2 adrenoreceptors located postsynaptically in the area postrema and reduction in the emetic impulses transmitted to the vomiting center of the brainstem reticular formation[43]. Eva Oddby-Muhrbeck et al[38], Carabine et al[44] and Joseph park et al[19] observed the antiemetic effect of Clonidine in their studies.

During the 24 hours observation period, there were no other side effects like ventilatory depression, hypotension, hypertension, bradycardia or tachycardia except for the sedation in the Clonidine group. Clonidine withdrawal phenomena characterized by hypertension and tachycardia did not develop in any of the patients in the Clonidine group. Clonidine withdrawal phenomena usually occurs after abrupt cessation of chronic treatment but not after a single dose[45].

# CONCLUSION

Oral Clonidine and oral Atenolol significantly reduces the tachycardia and hypertension associated with laryngoscopy and endotracheal intubation Clonidine provides better sedation and decreases the incidence of postoperative nausea and vomiting.

# BIBLIOGRAPHY

1) THOMAS J. GAL , Airway management, section III, chapter 42,
page 1636 in MILLER'S ANESTHESIA, Sixth edition.

2) PRYS ROBERTS C., GREENE LT., MELOCHE R., FOEX P. studies of anaesthesia in relation to hypertension. Hemodynamic consequences of induction and endotracheal intubation.
British journal of anaesthesia 1971; 43: 531- 545.

3) STOELTING RK. Blood pressure and heart rate changes during short duration laryngoscopy for tracheal intubation. Influence of
viscous or IV lidocaine. Anaesth Analg. 1978 ; 57: 197-199.

4) KAUTTO UM. Attenuation of the circulatory response to laryngoscopy and intubation by Fentanyl.
Acta Anaesth Scand 1982; 26: 217-21.

5) BLACK JE., KAY B. AND HEALY T. Reducing hemodynamic responses to laryngoscopy and intubation. A comparison of alfentanil with fentanyl. Anaesthesia 1984 ; 39 : 883-87.

6) STOELTING RK. Attenuation of blood pressure response to laryngoscopy and endotracheal intubation with sodium nitroprusside. Anesth Analg 1979 ; 58 : 116 – 119.

7) FENG CK, CHAN KH, LIU KN, OR CH, LEE TY. A comparison of lidocaine, fentanyl, and esmolol for attenuation of cardiovascular response to laryngoscopy and tracheal intubation. Acta Anaesthesiol Sin. 1996 Jun; 34(2): 61-7.

8) SAFAWAT AM, REITAN JA, MISLE GR AND HURLEY EJ. Use of propranolol to control rate-pressure product during cardiac anesthesia. Anesth Analg 60: 732-735.

9) DR. JAVAID A. ZARGAR , IMTIAZ A. NAQASH . comparative evaluation of the effect of metoprolol and esmolol on rate-pressure product and ECG changes during laryngoscopy and

endotracheal intubation in controlled hypertensive patients.
Indian J. Anaesth. 2002 ; 46 (5) : 365 – 368.

10) NISHIKAWA T, TAGUCHI M,KIMURA T, TAGUCHI N
SATO Y, DAI M. Effects of clonidine premedication upon
hemodynamic changes associated with laryngoscopy and tracheal
intubation. Masui. 1991 Jul; 40(7): 1083-8.

11) BEDFORD RF. Circulatory responses to tracheal intubation.
Probl Anesthesia 1998 ; 2: 201.

12) TOMORI Z. AND WIDDICOMBE JG. Muscular, bronchomotor and
cardiovascular reflexes elicited by mechanical stimulation of the respiratory tract . J physio 1969; 200 : 25 – 29.

13) ALBERTIN A, CASATI A, DENI F, DANELLI G, COMOTTI L, GRIFONI F AND FANELLI G. Clinical comparison of either small doses of fentanyl or remifentanil for blunting cardiovascular changes induced by tracheal intubation. Minerva Anestesiol. 2000 Oct;66(10):691-6.

14) TAM S, CHUNG F, CAMPBELL M. Intravenous lidocaine: optimal time of injection before tracheal intubation. Anesth Analg 1987; 66 : 1036 – 8.

15) GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 9 TH EDITION, 1996, MCGRAW HILL PUBLICATION.

16) LAURITO CE, BAUGHMAN VL, BECKER GL, DESILVA TW AND CARRANZA CJ. The effectiveness of oral clonidine as a sedative/anxiolytic and as a drug to blunt the hemodynamic responses to laryngoscopy. J Clin Anesth. 1991 May-Jun;3(3):186-93.

17) IAN R THOMSON, MARK D PETERSON AND ROBERT J HUDSON. A comparison of clonidine with conventional preanaesthetic medication in patients undergoing CABG. Anesth Analg 1998 ; 87 : 292-9.

18) BYRON C. BLOOR AND WERNER E. FLACKE. Reduction in halothane anesthetic requirement by clonidine, an alpha-adrenergic agonist. Anesthesia and Analgesia 1982 Sep;61:741-5.

19) JOSEPH PARK, JAY FORREST, RICK KOLESKAR, DOLLY BOLLA AND CHRIS CHU. Oral clonidine reduces postoperative PCA morphine requirements. Canadian Journal of Anaesthesia 1996/ 43:9/ 900-6.

20) HORN EP, WERNER C, SESSLER DI, STEINFATH M.
Late intraoperative clonidine administration prevents postanesthetic
shivering after total intravenous or volatile anesthesia.
Anesth Analg 1997 Mar ; 84(3):613-7.

21) HANDA F, TANAKA M, NISHIKAWA T, TOYOOKA H.
Effects of oral clonidine premedication on side effects of
intravenous ketamine anesthesia: a randomized, double-blind,
placebo-controlled study. J Clin Anesth 2000 Feb; 12(1): 19-24.

22) DIPAK L. RAVAL, MALINI K. MEHTA . oral clonidine premedication for attenuation of hemodynamic response to laryngoscopy and intubation. Indian J. Anaesth. 2002 ;46(2):124-129.

23) KING BD, HARRIS LC, STEIN FE, ELDER JD, DRIPPES RD. Reflex circulatory responses to laryngoscopy and tracheal intubation during general

anesthesia. Anesthesiology 1951;12:55-6.

24) CORBETT JL, KERR JH, PRYS ROBERTS C. cardiovascular disturbances in severe tetanus due to overactivity of the sympathetic nervous system . Anaesthesia 1969 ; 25 : 198-210.

25) FORBES AM, DOLLY FG. Acute hypertension during induction of anaesthesia and endotracheal intubation in normotensive men.
British Journal of Anaesthesia 1970 ; 42 : 618- 42.

26) GHIGNONE M, CALVILLO O, QUINTIN L. Anesthesia and
hypertension: the effect of clonidine on perioperative
hemodynamics and isoflurane requirements.
Anesthesiology 1987 Jul ; 67(1) : 3-10 .

27) POUTTU J, SCHEININ B, ROSENBERG PH. Oral premedication
with clonidine: effects on stress responses during general
anaesthesia . Acta Anaesthesiol Scand 1987; 31 : 730-4.

28) GHIGNONE M, NOE C, CALVILLO O, QUINTIN L. Anesthesia
for ophthalmic surgery in the elderly: the effects of clonidine on intraocular

pressure, perioperative hemodynamics, and anesthetic

requirement. Anesthesiology 1988 May ; 68(5) : 707-16.

29) STONE JG, FOEX P, SEAR JW, JOHNSON LL, KHAMBATTA HJ AND TRINER L. Myocardial ischemia in untreated hypertensive patients: effect of a single small oral dose of a beta-adrenergic blocking agent. Anesthesiology. 1988 Apr;68(4): 495-500.

30) SM HELFMAN, MI GOLD, EA DELISSER AND HERRINGTON. Which drug prevents tachycardia and hypertension associated with tracheal intubation: Lidocaine, Fentanyl, or Esmolol? Anesth Analg 72: 482-486.

31) FENG CK, CHAN KH, LIU KN, OR CH AND LEE TY. A comparison of Lidocaine, Fentanyl, and Esmolol for attenuation of cardiovascular response to laryngoscopy and tracheal intubation.

Acta Anaaaesthesiol sin. 1996 Jun;34(2):61-7.

32) CHADHA R, PADMANABHAN V, JOSEPH A AND MOHANDAS K. Oral clonidine pretreatment for haemodynamic stability during craniotomy.

Anaesth Intensive Care.1992 Aug;20(3):341-4.

33) DORMAN BH, ZUCKER JR, VERRIER ED, GARTMAN DM AND SLACHMAN FN. Clonidine improves perioperative myocardial ischemia, reduces anesthetic requirement, and alters hemodynamic parameters in patients undergoing coronary artery bypass surgery.
J Cardiothorac Vasc Anesth. 1993 Aug;7(4):386-95.

34) STUHMEIER KD, MAINZER B, CIERPKA J, SANDMANN W AND TARNOW J. Small, oral dose of clonidine reduces the incidence of intraoperative myocardial ischemia in patients having vascular surgery. Anesthesiology. 1996 Oct; 85(4) :706-12.

35) TETSU KIMURA, MAKOTO TANAKA AND TOSHIAKI NISHIKAWA. Effects of oral clonidine on heart rate changes after Neostigmine-Atropine administration. Anesthesiology. 88(6): 1507-1510, June 1998.

36) GRUNDMANN U., BERG K, STAMMINGER U., JUCKENHOFEL S. AND WILHELM W. Comparative study of pethidine and clonidine for prevention of postoperative shivering. A prospective, randomized, placebo-controlled double-blind study.
Anasthesiol Intensivmed Notfallmed Schmerzther. 1997 Jan;32(1):36-42.

37) MICHAEL A. CAMPAGMNI, MICHAEL B. HOWIE, PAUL F. WHITE AND

THOMAS D. MCSWEENEY. Comparative effects of oral clonidine and intravenous esmolol in attenuating the hemodynamic response to epinephrine injection. Journal of Clinical Anesthesia, Volume 11, Issue 3, May 1999, Pages 208-215.

38 ) EVA ODDBY-MUHRBECK, STAFFAN EKSBORG, OLLE MUHRBECK AND PERR ARNE LONNQVIST. Effects of clonidine on postoperative nausea vomiting in breast cancer surgery. Anesthesiology. 96(5):1109-1114, May 2002.

39) PRYS- ROBERTS C., MELOCHE R., FOEX P. studies of anaesthesia in relation to hypertension I: cardiovascular responses of treated and untreated patients. Br J Anaesth 1971;34: 122-137.

40) KUMAR A, BOSE S, BHATTACHARYA A, TANDON OP AND KUNDRA P. oral clonidine premedication for elderly patients undergoing intraocular surgery. Acta Anaesthesiol Scand. 1992 Feb;36(2):159-64.

41) LAURITO CE, BAUGHMAN VL, BECKER GL, CUNNINGHAM F, PYGON BH AND CITRON GM. Oral clonidine blunts the hemodynamic responses to brief but not prolonged laryngoscopy. J Clin Anesth 1993 Jan-Feb;5(1):54-7.

42) BATRA YK, INDU B AND PURI GD. Attenuation of pulse rate and blood

pressure response to laryngoscopy and tracheal intubation by clonidine. Int J Clin Pharmacol Ther Toxicol. 1988 Jul;26(7):360-3.

43) KATSUYA MIKAWA, KAHORU NISHINA, NOBUHIRO MAEKAWA AND MIGIWA ASANO. Oral clonidine premedication reduces vomiting in children after strabismus surery.

CAN J ANAESTH. 1995/42:11/ pages 977-81.

44) CARABINE UA, WRIGHT PMC, MOORE J. preanaesthetic medication with clonidine: a dose-response study.

Br J Anaesth 1991;67:79-83.

45) WING L.M.H ET AL (1977). QUOTED FROM DAS A.K AND RUDRA R. Clinical efficacy of oral Clonidine as a preanaesthetic medicant. Indian Journal of Anaesthesia 1995; 43: 133-9.

46) BENHAMOU D, VEILLETTE Y, NARCHI P AND ECOFFEY C. ventilatory effects of premedication with clonidine.

Anesth Analg 1991;73: 799-803.

47) S.SINGH AND J.E. SMITH. Cardiovascular changes after the three stages of nasotracheal intubation. Br J Anaesth 2003; 91: 667-71.

48) J.L. TONG, D.R. ASHWORTH AND J.E. SMITH. Cardiovascular responses following laryngoscope assisted, fibreoptic orotracheal intubation. Anaesthesia, 2005, 60, pages 754-758.

49) CHAURASIA SK, KANE DG AND CHAUDARI LS. A comparative study of Clonidine versus a combination of Diazepam and Atropine for premedication in orthopaedic patients.
J Postgrad Med 1999; 45(3): 74-8.

50) USHA SAHA AND T.S.JAYALAKSHMI. Pressor response and hypertension. Indian J. Anaesth. 2003; 47(6) :443-449.

51) ORKO R, POUTTU J, GHIGNONE M, AND ROSENBERG PH. Effect of clonidine on hemodynamic responses to endotracheal intubation and on gastric acidity. Acta Anaesthesiol Scand. 1987May;31(4):325-9.

52) TOIVONEN J AND KAUKINEN S. Clonidine premedication: a useful adjunct in producing deliberate hypotension. Acta Anaesthesiol Scand. 1990 Nov;34(8):653-7.

**A comparative study of the efficacy of oral clonidine and oral atenolol in attenuating the hemodynamic response to laryngoscopy and endotracheal intubation.**

Department of Anaesthesiology,

Thanjavur medical college and hospital,

Thanjavur.

Patient's name : Address:

Age / sex :

I.P.Number :

Unit :

O.T:

Diagnosis : Surgery :

Anaesthesiologist : Surgeon :

History :

Medical history : Hypertension / diabetes mellitus / asthma / jaundice /

cerebrovascular disease / others

Drug history :

**Preanaesthetic evaluation :**

Height : Weight :

Pulse rate : Respiratory rate:

Blood pressure : Airway:

Cardiovascular system :

Respiratory system :

Other systems : ASA grade :

Investigations :

Blood Hb : Urine sugar and albumin :

Blood sugar Serum electrolytes :

BUN : Serum creatinine :

Blood group and type :

Chest X-ray PA view :

ECG in all leads :

| S.NO. | DRUG | DOSE | ROUTE | TIME |
|---|---|---|---|---|
| 1. | | | | |
| 2. | | | | |

**Sedation score : 0 / 1 / 2 / 3**

**Respiratory rate**:

Intra operative observation :

| TIME | PARAMETERS | | | |
|---|---|---|---|---|
| | Pulserate (bpm) | S.B.P( mm of Hg) | D.B.P(mm of Hg ) | M.A.P (mm of Hg) |
| PO | | | | |
| PI | | | | |
| LI | | | | |
| I-1 | | | | |
| I-3 | | | | |
| I-5 | | | | |

**Recovery : normal / delayed**

Post operative period :

| **Time** (hours) | Pulserate (bpm) | Blood Pressure (mm of Hg) | Respiratory rate (breaths per min.) | complications |
|---|---|---|---|---|
| 0 | | | | |
| 1 | | | | |
| 2 | | | | |
| 3 | | | | |
| 4 | | | | |
| 5 | | | | |
| 6 | | | | |
| 7 | | | | |
| 8 | | | | |
| 9 | | | | |
| 10 | | | | |
| 12 | | | | |
| 14 | | | | |
| 16 | | | | |
| 18 | | | | |
| 20 | | | | |
| 22 | | | | |
| 24 | | | | |

(Signature of the observer)